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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 03/08/04 RA

Office Action Summary	Application No.	Applicant(s)	
	10/057,558	CHAPMAN ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *4,5,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-20 and 23-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/25/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, 6-20 and 23-36, drawn to a recombinant viral nucleic acid wherein the recombinant viral nucleic acid is derived from a plant virus, classified in class 536, subclass 23.1; class 435, subclass 69.1.

II. Claims 1, 4, 6-18, 21 and 23-36, drawn to a recombinant viral nucleic acid wherein the recombinant viral nucleic acid is derived from an animal virus, classified in class 536, subclass 23.1; class 435, subclass 69.1.

III. Claims 1, 5-18 and 22-36 drawn to a recombinant viral nucleic acid wherein the recombinant viral nucleic acid is derived from bacterial virus, classified in class 536, subclass 23.1; class 435, subclass 69.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I-III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation, function and effects based upon the different types of viral genome from which the viral nucleic acids are derived. For example, bacterial viruses function in a different manner and to a different effect from animal viruses (e.g. bacteriophage T4 vs. HIV). Therefore, the inventions of these different and distinct Groups are capable of supporting separate patents.

Claims 1, 18, 33 & 35 link(s) inventions of Groups I-III. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, 18, 33 & 35. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper. Further, although the different groups comprise the same classification, the nonpatent literature search required for each of the groups is different depending upon the type of viral genome from which the recombinant viral nucleic acid is derived (e.g. positive strand plant viruses vs. bacteriophage).

During a telephone conversation with Thomas Gallegos on 2/18/2004 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-3, 6-20 and 23-36. Affirmation of this election must be made by applicant in replying to this Office action. Claims 4-5 and 21-22 are withdrawn from further consideration by the examiner, 37

CFR 1.142(b), as being drawn to a non-elected invention. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/359,299, filed July 21, 1999; Application No. 09/232,170, filed January 15, 1999; and Application No. 09/008,186, filed January 16, 1998. Applicant has made a reference to the prior application and included the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. However, for the reference to be complete, the current status of all nonprovisional parent applications referenced should be included. The current status of the applications relied upon has not been disclosed in the reference.

Claim Objections

Claims 1-3, 6-20 and 23-36 are objected to because of the following informalities: The base claims are drawn to nonelected subject matter in so far as reading on any recombinant viral nucleic acid. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-3, 6-20 and 23-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Base claims 1, 18, 33 and 35 are drawn to a "recombinant viral nucleic acid". The metes and bounds are unclear and indefinite because "recombinant" could for example read on a nucleic acid construct with a single nucleotide from a viral source. The term "recombinant viral nucleic acid" is not defined in the specification. It is thus unclear how much of a viral sequence is required for the nucleic acid to meet the limitation of being a "viral" nucleic acid.

In addition claim 2 is unclear and indefinite because it recites the term "derived from" when referring to the composition claimed in relation to an RNA plant virus. It is unclear the nature and number of steps required to produce a derivative of a plant virus. It would be remedial to amend the claim language to recite "obtained from" which implied a more direct process for obtaining the nucleic acid.

Claim 3 is unclear and indefinite because it is not a complete sentence. Apparently the claim is missing a verb. However, if for example the verb "is" were provided, the claim would still suffer from insufficient antecedent basis, because the phrase, "said...nucleic acid native to single-stranded, positive sense RNA plant virus", does not have antecedent basis in the base claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claim 1-3, 6-20 and 23-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention**.

The base claims are drawn to compositions and methods comprising nucleic acid constructs with a 5' untranslated leader sequence (UTR) and a second sequence encoding a protein targeted for production, where the leader sequence mediates increased production of the target RNA and/or protein. The invention is thus drawn to a genus of recombinant nucleic acids comprised of *any* UTR operatively linked to any target sequence encoding a desired protein, where presence of the leader sequence increases target RNA and/or protein production in any cell. Furthermore, the increased production can occur as a result of increased RNA expression or increased translation and/or increased stability of mRNA. Thus the rejected claims encompass an enormous genus of nucleic acids that must, in conformation with a coding sequence for a desired protein, retain structural/functional characteristics that confer on the fusion tanscript increased expression and/or increased translation.

In addition, the claims (9, 24, 36) are drawn to the target sequence and a coat protein, together comprising a fusion construct, whereby the coat protein ultimately facilitates production of the target protein throughout the host cell. Put another way, there is a structure-function correlation between the leader sequence, target sequence and increased production in a cell. Furthermore, claim 7 is drawn to an additional genus of sequences where the ATG start codon is moved downstream to a new site, thus creating an artificial leader sequence. These embodiments require an ability to envision which modifications of *any* existing 5' UTR will necessarily lead to enhanced expression of RNA and/or protein.

For example, the sequences necessary for optimal mRNA production can be anywhere from +25 to +54 nucleotides relative to the transcriptional start site for the TMV coat protein mRNA. (Shivprasad et al. Virology, 1999; 255:312-23, at 313, col. 2, ¶ 3). However, each structure (e.g. coat protein) would reasonably be expected to differ from one source to the next. Thus the critical parameters that would ultimately effect protein production, such as nucleotides necessary for mRNA production, could not be known for all combinations to which the claims are drawn (e.g. genus of leader sequences and coat proteins from any source). As each structure is delimited to a function of increasing protein production, one cannot envision which combinations would effectuate the desired result.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification does not disclose a sufficient number of species so as to indicate to one of ordinary skill in the art that applicant is in possession of the genera claimed. The specification provides a single example of a 5'UTR (rice α-amylase). In addition, a single example of a TMV coat protein is provided. Moreover, a single plant species (*Nicotania. benthamiana*) is transfected with the constructs used.

The prior art suggests that even with the well-characterized tobamovirus system there can be substantial differences in production of proteins and that building an effective vector is not a trivial exercise. (e.g. Shivprasad et al. Virology, 1999 ;255 :312-23, at 320 under Conclusions, and entire document). Furthermore, 5' leader sequences from different sources can function through different mechanisms. For example, TMV's 5' leader UTR promotes translation (i.e. protein production) through binding and recruitment of other factors. (Gallie, DR. Nuc. A. Res. 2002; 20(15):3401-11, Abstract). Therefore, the prior art reasonably suggests that constructs from different sources may operate by wholly different mechanisms, where one construct (combination) may result in increased production of heterologous proteins while another may not.

Moreover, the virus-based system may be host specific. In other words, not every construct will necessarily lead to increased production in any host cell. For example, applicants disclosed species, of α-amylase leader sequence and TMV coat protein subgenomic promoter may not necessarily increase protein production in a species of plants different from *N. benthamiana* or a different genus of host cell altogether.

While a TMV-based system may have a wide host range, such an assertion does not necessarily hold true for use of such a system with any UTR and any coat protein. For example, UTRs from TMV are infectious to tobacco plants but not peas. (Nicolaisen et al. FEBS, 1992 ; 303(2,3) :169-72, at 169, col. 2). Furthermore, certain leader sequences may not necessarily systemically infect a host plant, where the coat protein used is from a source other than TMV (e.g. Rhinovirus capsid protein). Therefore the prior art militates against accepting the assertion, that all species within the enormous genera claimed would necessarily inhere the required structure to function correlation.

Thus the disclosure, in light of the prior art, is not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all recombinant nucleic acids, fusion constructs and artificial leader sequences based on the teachings in the specification. Furthermore, an applicant for a patent involving a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-6, 8, 10-20, 23, 25-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Gallie et al. (Nuc. A. Res. 1987; 15(21):8693-71; whole document).

The claims are drawn to compositions and methods for enhancing protein production using a recombinant viral nucleic acid composition comprising a nonnative UTR and a target sequence. Furthermore, the construct can be derived from a plant virus, more particularly a single-stranded, positive sense RNA plant.

In addition the target sequence can comprise a fusion with a coat protein. Additional embodiments include plasmid and expression vectors comprising the nucleic acid constructs claimed.

Gallie et al. teach compositions and methods for enhancing mRNA expression (and protein production) *in vivo* using UTR from several plant viruses. (e.g. Abstract). More specifically, Gallie et al. teach the UTR (e.g. Ω leader sequence) from several different viruses (e.g. tobacco mosaic virus (TMV), turnip yellow mosaic virus (TYMV)) were manipulated *in vitro* after chemical synthesis and leader sequences were modified (i.e. mutagenized) to contain specific restriction sites. (e.g. p. 8695; p. 8699, Fig. 1). TMV is a single stranded, positive sense RNA plant virus. In addition the sequences used were foreign (i.e. non-native) to the host cells eventually transfected. (e.g. p. 8697; describing transfection of *Xenopus* oocytes and *E. coli*). Furthermore, with several of the constructs tested there was increased protein production. (e.g. p. 8703, Table 2). The target sequences tested were non-native chloramphenicol acetyltransferase

(CAT) or β-glucuronidase (GUS), each of which has enzymatic activity (i.e. an enzyme). (e.g. Abstract, pp. 8702, 8704).

In addition, Gallie et al. teaches that the constructs are mobilized into a plasmid expression vector, containing a tryptophan promoter, thus comprising a vector with the leader sequence and a promoter. (e.g. p. 8696). Furthermore, Gallie et al. teach that the expression vector used comprises TMV, minus the origin-of-assembly (i.e. less than infective viral genome). (e.g. p. 8696, ¶ 2). Therefore Gallie et al. anticipate the rejected claims.

4. Claims 1-3, 6, 8-20 and 23-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Jobling and Gehrke (Nature, 1987; 352:622-5; whole document; hereinafter Jobling).

Additional claims 9, 24 and 36 are drawn to the target sequence comprising a non-native sequence encoding a fusion protein with a coat protein.

Jobling teaches a non-native UTR from the coat protein of alfalfa mosaic virus (AMV), which is a positive, single strand RNA plant virus. (e.g. Abstract). More specifically, a chemically synthesized and modified (i.e. mutagenized) AMV leader sequence was subcloned into an expression plasmid(SP64) to target sequences of either IL1β, barley α-amylase or rabbit α-globin. (e.g. p. 623, Fig. 1, Methods). Therefore, Jobling teaches a construct *comprising* a first and second sequence, with a UTR, sequences encoding a coat protein and target protein, as a fusion construct. The various constructs were examined in a cell extract system (i.e. reticulocytes). Jobling teaches that the chimeric constructs can result in increased protein production (i.e. 35 fold increase). (e.g. Abstract, p. 624, Fig. 2).

With respect to applicant's claims drawn to isolated host cells transformed with recombinant viral nucleic acids, the claims are read as broadly as reasonable and in light of the definition provided for the term "host". (Spec. p. 26; defining host to include "[T]erm is intended to include...*in vitro* extracts thereof"). Therefore, claims drawn to host cells are also anticipated.

5. **Claims 1-6, 8, 10-20, 23 and 25-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Nicolaisen et al. (FEBS, 1992; 303(2,3):169-72; whole document; hereinafter Nicolaisen).**

Nicolaisen teaches compositions and methods for enhancing protein production. Specifically, Nicolaisen teaches using UTRs from both TMV and potyvirus in a fusion with a reporter protein (GUS) incorporated into expression plasmids. (e.g. p. 169, bridging ¶ to p. 170). Furthermore, Nicolaisen teaches that tobacco etch potyvirus UTR is mutagenized to insert two nucleotides into the UTR. (e.g. p. 170, col. 1, middle of 1st ¶). In addition, Nicolaisen teaches transformation of pea and tobacco protoplasts (e.g. p. 170, at 2.4), as well as truncations of UTRs (e.g. p. 171, col. 1, last ¶). The UTRs tested increased GUS expression in each of the cell systems tested. (e.g. p. 171, Fig. 2). Therefore, Nicolaisen anticipates the rejected claims.

6. **Claims 1-3, 6, 8-20 and 23-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Fitchen et al. (US 6,503,732 B1; whole document; hereinafter '732 patent).**

The '732 patent teaches compositions and methods where a modified construct, comprising a UTR and fusion protein comprising a heterologous protein with the TMV coat protein, is used for the expression of heterologous peptides in a host plant. More specifically, the

'732 patent teaches a construct with a positionally modified (i.e. non-native) TEV 5' untranslated region in a fusion with a foreign protein (i.e. NIa protein) and a coat protein (TMV CP). (e.g. Figs. 3A, 3B).

In addition, the coat protein is further modified in a fusion with heterologous proteins inserted in a region of the coat protein, thus modifying (*in vitro* mutagenesis) the coat protein (e.g. col. 9, ll. 25-35), thur producing a construct with less than an infective viral genome (col. 9, ll. 50-51). Furthermore plant host cells are transformed with the constructs and there is increased production of fusion proteins. (e.g. col. 4, ll.56-58; Fig. 4, col. 5, ll.54-60).

The '732 patent also teaches expression plasmids that comprise the viral constructs, where the plasmid vector contains an RNA promoter. (e.g. col. 14, bridging ¶ to col. 15). In addition, the constructs are used to express vaccines or antigenic epitopes. (e.g. col. 4, ll. 51-54; col. 16, ll. 40-45).

Therefore the '732 patent anticipates the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER